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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/622,419 | 08/16/2000 | Hartwig Schroder | 48792 | 3392 |

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| EXAMINER | |
|---|---|
| SAIDHA, TEKCHAND | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | 9 |

DATE MAILED: 10/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/622419 | Schroder |
| **Examiner** | **Group Art Unit** |
| T. Saidha | 1652 |

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***—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—***

**P ri d f r Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE -3- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

☒ Responsive to communication(s) filed on 8/18/03 (Paper #8).

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

**Disposition of Claims**

☒ Claim(s) 1 & 3-6 & 15 is/are pending in the application.

Of the above claim(s) 15 ~~is~~/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1 & 3-6 ~~is~~/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119 (a)-(d)**

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been ☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

**Attachment(s)**

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

**Office Acti n Summary**

1. Applicants' amendment and reply filed 8.18.02 (Paper No. 8) is acknowledged. Claims 1 & 3-6 are pending and under consideration in this examination.

2. Claim 15 is not being considered along with the processes claims because of the prior Lack of Unity of Invention, and according to which - Claims 1-6 & 12 (in-part) drawn to a process of producing biotin using a host organism transformed with the gene sequence of **SEQ ID NO : 1** [SAM-synthase] and the biotin synthesis gene of **SEQ ID NO : 3** [bioS1] were under consideration.

3. Applicants are reminded again that SEQ ID NO : 5 & 7 or similarly unrelated language is not under consideration, and that subject matter of inventions of Groups not under consideration be deleted, for example, current claims 1 & 3-6.

4. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

5. ***Enablement Rejection***

Claims 1 & 3-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for producing biotin which comprises expressing a S-adenosylmethionine synthase gene of SEQ ID NO: 1 and a biotin biosynthesis gene of SEQ ID NO : 3 in a prokaryotic or eukaryotic host organism able to synthesize dethiobiotin, does not reasonably provide enablement for using any of the functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3 (claims 1, 3-6 & 12), or wherein the deduced amino acid sequences of the gene sequences of SEQ ID NO : 1 & 3 have a homology of 50-100% and enable increased biotin production, or express the variously modified sequences in various host organisms irrespective of

the host being capable of producing biotin, or its expression in regulation-defective biotin mutants (claims 3-6), either alone or in shared vector or on separate vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicants have described a single construct of co-expression of the combination of metk (SEQ ID NO : 1) and bioS1 (SEQ ID NO : 3) from *Escherichia coli* (see pages 15 of the instant specification). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims are so broad as to encompass a process of using a modified gene of SEQ ID Nos. 1 & 3 for biotin production, wherein the sequences are modified by any extent and includes deletion, substitution or insertion (functional variants or analogs); prokaryotic or eukaryotic homologs from bacteria, fungi, plant, animal or human (functional analogues)and truncated sequences thereof; or derivatives (claims 1, 3-6), or wherein the sequences are modified to having sequence homologies of 50-100% (claim 2) (*see* Specification, page 5, lines 22-47 for Applicants definitions). Applicants have neither disclosed nor described, or exemplified the numerous proposed modifications encompassed by the claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the extremely large number of SAM-synthase and/or biotin biosynthesis genes broadly encompassed by the process claims. Since the amino acid sequence of a protein

determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequences of SEQ ID Nos. 1 & 3 from which amino acid sequences can be deduced.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of SEQ ID Nos. 1 & 3 or that ranging in homology from 50-100% identity to the encoded amino acid sequences, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting enzyme activity; (B) the general tolerance of enzyme to modification and extent of such tolerance; © a rational and predictable scheme for modifying any enzyme residues with an expectation of obtaining the desired biological

function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including method or process of using said enzyme(s) with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of process of using such enzymes (SAM-synthase & biotin biosynthesis enzyme) having the desired biological characteristics or its co-expression into any host which may include a host cell not capable of biotin production, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue in using the modified enzyme in the method claimed. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants Arguments :

Applicants citing specification page 5, lines 23-29, argue that the specification clearly indicate that a number of other enzymes are known to have the ability to assume the enzymic activity of bioS1, bioS2 & bioS3. Given the broad range of genes known in the art to be suitable substitutes, the ability of one skill in the art to recognize and use functional equivalents is relatively high - accordingly the homology range now recited in claim 1 is enabled.

In response, first it is again emphasized that bioS1 or SEQ ID NO : 3 & SEQ ID NO : 1 is under consideration. Further, it is not clear what broad range of genes are known as suitable

substitutes. What substitutes are functional equivalents ? And how Applicants have arrived at the conclusion that the homology range of 50-100% is now enabled ? Clearly the specification provides no guidance to any enablement issues or written description issues as indicated by the Applicants. Applicants have clearly, either in-part or wholly not addressed many of the issues pertaining to enablement or written description rejections presented in the prior Office Action.

6. ***35 U.S.C. § 112, first paragraph (Written Description)***

Claims 1 & 3-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1 & 3-6 recite 'functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3. However, description to any such functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3 is lacking (claims 1 & 3-6).

Further claim 1, recite '50-100% homology to the deduced amino acid sequences of SEQ ID Nos. 1 & 3 The specification, however, only provides a process for using a single representative species of a combination of full length gene sequences from *E. coli* of SEQ ID Nos. 1 & 3 for biotin production. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species to other species where such sequences are conserved in order to establish a relationship among species or modify the enzyme by substitution, insertion or deletion (analogues, variants or derivatives) or make a polypeptide 50-100 % identical to the encoded amino acid

sequences deduced from the gene sequences SEQ ID Nos. 1 & 3 and have desired biological activities for biotin production. The specification also fails to describe additional representative species of these combinations by way if modifications such as that claimed by any identifying structural characteristics other than the properties or activity recited in claims, for which no predictability of structure is apparent. Further, description of expressing SEQ ID Nos. 1 & 3 into any prokaryotic or eukaryotic host organism either alone, or on shared vector or on separate vectors is also lacking. Given this lack of additional representative species, such as the proposed modifications of SEQ ID Nos. 1 & 3 and still retain functional characteristics of a process of producing biotin, or various host cells or the expression into single or shared vector, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicants Arguments : No specific arguments presented.

7. Double patenting rejection made in the prior Office action, being no more relevant to the amended claims, is hereby withdrawn.

8. ***Allowable Subject matter*** (an example)

Claim 1 : A process for producing biotin which comprises expressing a S-adenosylmethionine synthase gene of SEQ ID NO: 1 and a biotin biosynthesis gene of SEQ ID NO : 3 in a prokaryotic or eukaryotic host organism able to synthesize dethiobiotin, culturing the host organism, separating off the biomass followed by purification and recovery of the biotin.

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

T C Saidha

**Tekchand Saidha**
**Primary Examiner, Art Unit 1652**
**October 3, 2003**